Clinical study report

Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage (The PATCH Study)

A multi-centre randomised, double-blind, placebo-controlled trial of prehospital treatment with tranexamic acid for severely injured patients at risk of acute traumatic coagulopathy.

Investigational Product: Tranexamic acid (TXA)

Indication: Severe injury with risk of acute traumatic coagulopathy (ATC) and bleeding

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Principal Investigator:

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Study initiation date: 29-04-2021 (FPI)
Study completion date: 25-03-2022 (LPO)

Signatures

The undersigned authors agree to the contents of this final report by their signatures. The clinical trial was conducted in accordance with the EU recommendations on "Good Clinical Practice (GCP)" including the archiving of essential documents, the Declaration of Helsinki and in accordance of the Medicines law and regulations.

Sponsor (authorized representative UW/H)	Dr. René Geißen; ZKS UW/H	20.04.2023 Datum
Principal Investigator	Prof. Marc Maegele, Cologne-Merheim Medical Centre	24/04/2023 Datum
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Synopsis

(max. 3 Seiten)

Sponsor: Witten/Herdecke University	
Investigational Product: Tranexamic acid (TXA)	
Name of Active Ingredient: Tranexamic acid (TXA)	
Title of Study: A multi-centre randomised, double-blind, placebo-controlled trial of prehospital treatment with tranexamic acid for severely injured patients at risk of acute traumatic coagulopathy.	
Principal Investigator: Professor Dr. med. Marc Maegele	
Study Center: 1. Kliniken der Stadt Köln Klinik für Orthopädie, Unfallchirurgie und Sporttraumatologie Ostmerheimer Str. 200, Köln, 51109, Germany 2. Universitätsklinikum Frankfurt Klinik für Unfall-, Hand- und Wiederherstellungschirurgie Theodor-Stern-Kai 7, Frankfurt am Main, 60590, Germany 3. BG Unfallklinik Frankfurt am Main Abteilung für Unfallchirurgie und Orthopädische Chirurgie Friedberger Landstraße 430, Frankfurt am Main, 60389, Germany	
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first patient in: 29.04.2021 (FPI Germany; 28.07.2014 FPI Australia) **last patient out:** 25-03-2022	**Phase:** III

Aim of study:

1. The proportion of patients with a favourable outcome at 6 mo (moderate disability - good recovery, GOSE scores 5-8) compared to those who have died (GOSE 1), or have severe disability (GOSE 2-4).
2. Units of blood products used in the first 24 h (pRBCs, FFP, platelets, PCC, FVIIa, cryoprecipitate/fibrinogen); blood lactate on patient arrival at hospital; fibrinolytic, coagulation, inflammatory and haematological profile at hospital arrival, at end of treatment with study drug (i.e. immediately after administering the second dose of the study drug by 8 h infusion), and at 24 h after the first dose of study drug (i.e. 24 h from the pre-hospital bolus dose); vascular occlusive events (acute myocardial infarction (AMI), stroke, DVT, pulmonary embolism (PE)) until 28 d or hospital discharge whichever occurs first; ventilator-free days within first 28 d; mortality at 24 h, 28 d and 6 mo; proportion of deaths due to bleeding, vascular occlusion (PE, stroke, AMI) and multi-organ failure (MOF); cumulative incidence of sepsis up to 28 d or hospital discharge whichever occurs first and quality of life (WHODAS 2.0, EQ5-D) at 6 mo.

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***Methods*:** **Experimental intervention:** As soon as possible after injury, emergency medical services (EMS) clinicians administered 1 g Tranexamic Acid (TXA; 10 ml ampoule containing 100 mg/ml TXA in water for injection) via iv injection. After the patient arrived at hospital, clinicians administered 1 g TXA (10 ml ampoule containing 100 mg/ml TXA in water for injection) added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h. **Control intervention:** As soon as possible after injury, EMS clinicians administered a 10 ml ampoule containing 0.9 % w/v Sodium Chloride via iv injection (ampoules containing Sodium Chloride appear identical to ampoules containing TXA). After the patient arrived at hospital, clinicians administered a second 10 ml ampoule containing 0.9 % w/v Sodium Chloride added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h. **Sampling:** Blood samples were collected on hospital arrival, on treatment completion with the study drug (i.e. end of 8 h infusion), and at 24 h after initial treatment with the study drug. Epidemiological, clinical, treatment and outcome data including use of blood/haemostatic agents were collected. Participants underwent daily sepsis screening over 28 d and venous thrombosis screening 5-7 d after injury. **Follow-up**: At 6 month after enrolment, patients were contacted for telephone interviews to assess QoL using the following standardised structured telephone questionnaires: Glasgow Outcome Score Extended (GOSE); EQ5-D; WHODAS 2.0 (12 item version).
Number of patients: Planned 1316 (in the member state - Germany: 250) Analysed 1307 (Germany: 8 randomised and analysed)
Diagnosis und Inclusion criteria: Injured patients who are at risk of ATC and who are treated in advanced trauma systems. 1. Adult patients (age ≥18 ≤45 years); 2. Injured through any mechanism; 3. COAST score ≥3; 4. First dose of study drug can be administered within three hours of injury; and 5. Patients to be transported to a participating trauma centre.
Test product: Tranexamic Acid (TXA) **Dose**: 1 g TXA (in 10 ml water) and 1g TXA (in 1000 ml 0.9 % NaCl) **Mode of administration**: slow intravenous injection and infused intravenously
Duration of treatment: The study duration for each study participant was 6 months (28 days plus telephone interview 6 months after the accident).
Reference Product: Placebo **Dose:** 10 ml 0.9 % NaCl and 1000 ml 0.9 % NaCl **Mode of administration:** slow intravenous injection and infusion intravenously
Statistical methods: Analyses used the intention-to-treat principle. The primary outcome, favourable – unfavourable neurological outcome dichotomy at six months, compared between treatment groups using a risk

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ratio and 95 % confidence interval estimated by log-binomial regression models adjusting for the randomization stratification variables. If model convergence was not achieved then poisson regression with robust standard error was applied. The impact of any baseline imbalances was assessed by adding the relevant terms to the risk ratio regression models and was regarded as sensitivity analyses. Assessment of heterogeneity of treatment effect across pre-specified subgroups was incorporated interaction term in the regression models.

For binary secondary outcomes, the same approach was applied as for the primary endpoint. A proportional odds cumulative logit model, adjusting for relevant covariates, was applied to the eight-level ordinal 6-month GOSE endpoint. Analysis of right-skewed outcomes were log-transformed and analysed using linear regression with robust standard errors, and symmetrically distributed endpoints were analysed with linear regression without logarithmic transformation. Ventilator-free-days to day 28 and left-skewed outcomes were analysed using quantile regression.

Summary - Conclusion:

In adults with major trauma and suspected acute traumatic coagulopathy, pre-hospital administration of tranexamic acid followed by an infusion over 8 hours did not improve the rate of survival with a favorable functional outcome at 6 months compared with placebo.

Safety Results:

A concern about tranexamic acid has been the potential risk of thrombotic complications, the prevention of which is a major focus of trauma care. We screened inpatients for lower limb deep vein thrombosis and, in contrast to a previous trial of tranexamic acid in major trauma patients [6] and another trial of tranexamic acid in non-traumatic gastrointestinal bleeding,[13] found little evidence that tranexamic acid increased the risk of such events.

Efficacy Results:

A total of 1310 patients were recruited by 15 emergency medical services in Australia, New Zealand, and Germany with 661 patients assigned to tranexamic acid and 646 assigned to placebo. Survival with a favorable functional outcome at 6 months occurred in 307 of 572 (53.7%) patients in the tranexamic acid group and 299 of 559 (53.5%) in the placebo group (risk ratio (RR) 1.00; 95% confidence interval [CI], 0.90 to 1.12; P=0.95). At 28 days after injury, death had occurred in 113 of 653 patients (17.3%) in the tranexamic acid group and in 139 of 637 (21.8%) in the placebo group (RR 0.79; 95% CI 0.63-0.99) and, by 6 months, death had occurred in 123 of 648 (19.0%) patients in the tranexamic acid group and in 144 of 629 (22.9%) in the placebo group (RR 0.83; 95% CI 0.67 to 1.03). The number of serious adverse events, including vascular occlusive events, did not differ meaningfully between the groups

Conclusion:

In conclusion, in adults with major trauma who are at risk of acute traumatic coagulopathy and are receiving treatment within advanced trauma systems, 1 g of intravenous tranexamic acid initiated in the pre-hospital setting and followed by an infusion of 1 g of tranexamic acid over 8 hours in hospital did not increase the rate of survival with a favorable functional outcome at 6 months compared to placebo.

The data analysis includes data from Australia, New Zealand and Germany. No separate analysis was carried out for Germany.

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